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REVIEW

Tumour Recurrence or Treatment Sequelae Following Radiotherapy for Larynx Cancer

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Differentiating between recurrent carcinoma and significant sequelae of radiotherapy after treatment of laryngeal carcinoma is an uncommon but difficult clinical problem. Head and neck surgeons can be faced with deciding on the necessity for salvage laryngectomy without prior histological confirmation of recurrence. This paper reviews the literature pertaining to this topic to provide a better overall estimate of the risk of recurrence in these cases. Approximately 50% of patients with severe oedema or necrosis following radiotherapy for larynx cancer will have recurrence. Less than 10% of all larynges removed will be histologically negative when persistent or recurrent tumour is suspected clinically or indicated by biopsy following radiotherapy. © 1996 Wiley-Liss, Inc.

KEY WORDS: **Oedema, necrosis, salvage, laryngectomy**

INTRODUCTION

Vigilant follow-up evaluation of patients after radiotherapy for laryngeal carcinoma is of particular importance as surgical salvage may be possible if recurrent or persistent disease is detected. Early detection under some circumstances may even allow partial laryngectomy to be performed [1]. Postradiotherapy changes in the form of oedema or necrosis, present a dilemma for the radiation oncologist, but more so for the head and neck surgeon in trying to differentiate between radiotherapy effects and tumour recurrence. A decision on the necessity for total laryngectomy may be required even where biopsy has not produced histological confirmation of recurrence. The need for biopsy itself can present a dilemma as this may exacerbate postradiotherapy changes, although if clinical suspicion of recurrence exists a biopsy should be performed. Management of these difficult cases could be assisted if the proportion of patients likely to harbour recurrent disease in the presence of oedema or necrosis after radiotherapy was known. Much of the radiotherapy literature relates to the incidence of late effects, rather than to the issue of distinguishing these from recurrent disease [2].

At the outset it should be stated that a number of variables create difficulties in drawing conclusions from the literature in relation to postradiotherapy laryngeal edema and/or necrosis. There is interclinician variability in the definition of "significant" oedema. Reports have been inconsistent in using oedema or necrosis as an endpoint, sometimes interchanging or using both clinical descriptions. Necrosis is usually not defined and may represent a spectrum of clinical scenarios, including soft tissue necrosis or osteochondronecrosis, or both. Perichondritis has also been used to describe a variety of symptoms and clinical findings [3–5]. There is interclinician variability in the indications for biopsy, tracheostomy, and laryngectomy, and variations between centres may be even greater. Related to this is the pathological interpretation of biopsy after radiotherapy and its reliability (i.e., sensitivity and specificity). None of this information will, however, accurately estimate the surgeon's clinical sensitivity and specificity in predicting that underlying carcinoma is present in a previously irradiated larynx. In the final analysis this probably represents the most important estimate of all.

The literature relevant to this topic spans many years

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during which radiotherapy treatment techniques, total doses, and fractionation schedules have changed as the influence of fractionation and overall treatment time on dose response has become apparent. Many reports have dealt only with patients having significant postradiotherapy problems or where laryngectomy has been required, with the original total denominator of patients receiving radiotherapy unknown [6,7]. Treatment parameters vary depending on laryngeal subsite and stage. Coming to definitive conclusions about which of these interrelated patient and treatment variables are significant is also difficult. These are discussed but not reviewed in detail, as they are beyond the scope of this paper.

EFFECT OF RADIOTHERAPY ON THE LARYNX

During and immediately following radiotherapy, acute changes occur that are clinically most apparent in the mucosa. There is basal mucosal cell damage with eventual desquamation and ulceration occurring depending on the total dose of radiation and fractionation schedule. Hyperemia and oedema occur and, where ciliated epithelium exists, its function can be impaired with retention of thickened secretions [4,8].

Oedema and necrosis following radiotherapy are generally categorised as late effects. The pathological processes leading to late reactions should be differentiated from those responsible for acute effects. These late effects are largely due to vascular changes and fibrosis, which may have an impact on the vascular and lymphatic competence of the larynx. Atrophy of the mucosa and its supporting stroma occur [9]. The precise pathophysiology leading to laryngeal oedema is not well understood, but impaired vascular and lymphatic outflow together with increased vascular permeability have been postulated [8]. The cascade of events that lead to late radiation effects is only now starting to unfold [10]. The laryngeal skeleton is also important when considering chondronecrosis or what, in some cases, may be osteonecrosis. Adult cartilage has no blood vessels and no lymphatics and very few mitotically active cells, making it intrinsically resistant to the effects of radiation. All of the cartilaginous response is related to the perichondrium, which is the proliferative component. Cartilage changes rarely occur in the absence of mucosal breakdown, infection, or inflammation. The laryngeal cartilages calcify and ossify in adults, thus developing a blood supply and a marrow cavity, and this may have some role to play in the development of necrosis [5,8,11]. Unlike cartilage, radionecrosis of bone can take place beneath intact mucous membranes. The arytenoids are often the most densely and completely calcified, and are the cartilages most frequently involved when chondronecrosis occurs in association with radiotherapy [5].

TIME COURSE AND INCIDENCE OF LARYNGEAL OEDEMA FOLLOWING RADIOTHERAPY

Laryngeal oedema can occur acutely during radiotherapy and persist following its completion or, less commonly, develop in the otherwise normal-appearing larynx after radiotherapy. Table I outlines the time course and incidence of laryngeal oedema following radiotherapy in four series where this was specifically reported. Although a broad spectrum of tumour sites, treatment techniques, and doses is represented, the data are consistent. The British Institute of Radiology (BIR) studies show a higher proportion of patients with persisting oedema in the first 3 months following radiotherapy, but this may simply reflect the difference between prospective and retrospective assessment of treatment-related toxicity [12]. It appears that up to one-fourth of patients will have oedema during this immediate postradiotherapy time frame. Beyond 6 months, these and other series in which due attention has been paid to technique and treatment volume, indicate 0–6% of patients will have persisting oedema [13–19]. For the subgroup of early-stage (T1, T2) glottic cancers, the incidence is lower again, with 0–2% of patients developing significant persistent oedema [14–16,18].

TIME COURSE AND INCIDENCE OF LARYNGEAL NECROSIS FOLLOWING RADIOTHERAPY

Laryngeal necrosis following radiotherapy, as has already been stated, is sometimes reported in isolation, but often in conjunction with severe oedema as a clinical endpoint of interest. Rarely does the incidence rise above 1%, particularly in more recently reported series [12,18,20–25]. Fletcher et al. [16] noted the importance of the era of treatment on the incidence of severe laryngeal oedema or necrosis. For patients treated before 1960, this incidence approached 9% and was less than 1% for patients treated during 1961–1970. A similar effect occurred in the BIR studies, in which the incidence of necrosis in patients treated during 1975–1985 was reduced by a factor of 2, compared with those treated during 1966–1975 [12,21]. As in the case of oedema, large numbers of patients have been treated in individual series with excellent tumour control rates and a 0% incidence of necrosis [14]. The incidence of necrosis and edema as late sequelae of radiotherapy peaks during the 12 months following treatment, unfortunately contemporaneous with the peak incidence of recurrence [3,26]. Late necrosis occurring many years after radiotherapy has also been reported but is extremely rare [27].

OEDEMA OR NECROSIS HARBOURING UNDERLYING RECURRENCE

Table II details the experience from 11 series reporting laryngeal edema and/or necrosis following radiotherapy

TABLE I. Time Course and Incidence of Laryngeal Oedema Following Radiotherapy for Laryngeal Cancer

Series	No. of patients	Patients with laryngeal oedema					
		>3 mo		>6 mo		>12 mo	
		N	%	N	%	N	%
Fu et al. [31]	247	38	15	—	—	7	3
Stewart [44]	419	—	—	26	6	—	—
Wiernik et al. [12]	713	199	28	35	5	25	3
Wiernik et al. [21]	611	173	28	—	—	—	—

TABLE II. Laryngeal Cancer: Oedema or Necrosis and Proportion With Underlying Cancer

Series	Site ±stage		No. of patients	Clinical endpoint (i.e., oedema/ necrosis)	No. with oedema/ necrosis	Patients with recurrence	
						N	%
Wiernik et al. [12,20]	Laryngopharynx	T1–T4	713	Necrosis	14	10	(71)
Wiernik et al. [21]	Laryngopharynx	T1–T4	611	Necrosis	5	3	(60)
Stell and Morrison [26]	Larynx		NS	Necrosis	12	4	(33)
Mills [45]	Glottic	T1–T3	96	Oedema	13	6	(46)
Fu et al. [31]	Glottic	T1–T4	247	Oedema >3/12	38	17	(45)
Mintz et al. [3]	Larynx	T1–T4	348	Perichondritis or chondronecrosis	52	26	(50)
Turner and Tiver [46]	Larynx	T1–T4	141	Oedema	9	5	(55)
Henk [29]	Larynx	T3–T4	NS	Gross oedema requiring tracheostomy	6	4	(67)
Henk [29]	Larynx	T3–T4	NS	Moderate oedema	11	6	(55)
Kagan et al. [6]	Glottis	T1–T4	NS	Oedema >6 mo	41	19	(46)
Flood and Brightwell [28]	Larynx	T1–T4	NS	Severe oedema causing stridor or requiring tracheostomy	7	5	(71)
Stevens et al. [47]	Glottis	T1–T4	127	Oedema	3	0	(0)
					211	105	(50)

NS, not stated.

and the proportion of cases subsequently found to have underlying malignancy. In some cases biopsy eventually confirmed the presence of recurrence and in others a laryngectomy was performed either without a prior biopsy or if the clinical circumstances so dictated. No attempt has been made to separate these two approaches as information about prelaryngectomy biopsy was often not available, and the overall data are believed to present a more important clinical picture. Of the 211 patients developing significant oedema or necrosis following radiotherapy, 50% (105) were eventually found to have underlying recurrence.

In the 5 series that used necrosis or severe oedema (that causing stridor or requiring tracheostomy) as the endpoint of interest, 59% of patients had underlying recurrence [12,21,26,28,29]. There is a significant range (0–71%), however, in the proportion of patients with recurrence. This probably reflects more on the "softness" of oedema as a clinical endpoint as the majority of data are remarkably consistent. What is also clear is that, although these clinically challenging cases are prominent in the memories of many clinicians, they represent a very small proportion of the total number of patients undergoing radiotherapy for laryngeal cancer.

LARYNGECTOMY WITH SUBSEQUENT NEGATIVE HISTOLOGY

Owing to a number of clinical circumstances, the surgeon may proceed with laryngectomy in a patient previously irradiated. This may be because of a positive biopsy, a high clinical suspicion of recurrence or if the functional status of the larynx is so poor as to necessitate its removal. A possible indirect measure of the disparity in attitudes toward salvage (and perhaps to a lesser extent the incidence of significant radiotherapy complications) is the proportion of larynges removed for salvage following radiotherapy that contain no evidence of tumour. The possibility of "biopsy cure" cannot be excluded for some

TABLE III. Salvage Laryngectomy and Subsequent Negative Histology

Series	No. of salvage laryngectomies	Histology negative	
		N	%
Alcock et al. [30]	151	12	8
Viani et al. [22]	103	12	12
Mendenhall et al. [13,15]	53	4	8
Crellin et al. [25][a]	50	11	22
Fu et al. [31]	59	1	2
Turner and Tiver [46]	26	4	15
Stevens [47]	14	3	21
Keene et al. [5][b]	184	11	6
Bahadur et al. [32]	52	2	4
Flood and Brightwell [28]	18	2	11
Jose et al. [48]	22	0	0
Croll et al. [49]	16	0	0
	748	62	8

[a]Excludes patients treated with neutrons.
[b]Excludes patients with planned preoperative radiotherapy and autopsy cases.

of these cases but seems an unlikely explanation for the majority. Table III shows the data from 12 series in which the proportion of histologically negative larynges removed was reported. The overall figure of 8% is largely determined by the seven series with 50 or more cases [5,13,15,22,25,30–32]. These 7 series account for 87% of all the cases included in this review. Again, there is a significant range of 0–22%. As previously indicated, there are unknown and probably inherent sources of bias in such data. It may be only representative of patients undergoing close follow-up and subject to publication bias. If these data are taken at face value, head and neck surgeons performing significant numbers of salvage procedures after radiotherapy will, on average, remove one larynx containing no evidence of tumour for every 11 with tumour. For select subgroups at high risk of developing late radiotherapy sequelae, such as T3 glottic tumours, the proportion of histologically negative specimens will be even higher [13].

BIOPSY AND THE SURGEON'S OPINION IN PREDICTING RECURRENCE

A biopsy is often performed in assessing the irradiated larynx when recurrence is considered possible and the histological interpretation of these specimens can be notoriously difficult. The reliance placed on the results by different surgeons may vary, as alluded to above. One series reporting a patient who had 7 direct laryngoscopies with biopsy before a decision on laryngectomy was made, can be contrasted with another in which 52 salvage laryngectomies were performed without prior biopsy [28,32]. Viani et al. [22] analysed the sensitivity and specificity of preoperative histologic diagnosis in patients previously irradiated. These investigators found high sensitivity (97%) for positive results (i.e., cancer being present), but a low specificity (25%). Similarly, the negative predictive value was 50%. Of 6 patients with preoperative negative histology who proceeded to laryngectomy, 3 were found to have underlying cancer. Crellin et al. [25] attempted to assess the accuracy of the surgeon's opinion that cancer was present. They found a sensitivity of 98%, but the specificity was 46%. These results would suggest the opinion of an experienced head and neck surgeon is equal to that of a positive histological diagnosis in correctly predicting that recurrence has occurred. Unfortunately, the problem lies where histology is negative or the surgeon feels underlying malignancy is not present. Under these circumstances, a correct diagnosis is at best made in 50% of cases. It is interesting that this is similar to the proportion of patients who have underlying recurrence in the presence of severe oedema or necrosis after radiotherapy (Table II). Clearly there are changes other than just the presence or otherwise of oedema or necrosis which influence the decision to proceed with biopsy or in turn increase the surgeon's suspicion that recurrence is present.

One large randomised study used routine biopsy at 8–12 weeks following completion of radiotherapy to evaluate two different treatment approaches and the value of the biopsy itself [33]. A negative biopsy predicted for ultimate local control in 83/118 (70%) cases. It is not stated whether a false-positive rate was associated with biopsy.

VOCAL CORD MOBILITY AFTER RADIOTHERAPY

In general, recurrence is present in the patient with a mobile cord after radiotherapy that subsequently becomes fixed. However, there are reports of patients developing a fixed cord without other signs of recurrence and with further follow up remained free of disease [34]. The association of fixation or refixation with oedema implies a much higher risk of recurrence [28]. Two series reporting the results of radiotherapy for patients with cord fixation (T3) indicate that persisting fixation after treatment does not necessarily imply a higher incidence of recurrence [17,29]. In the Florida series, for patients assessed 1 month following radiotherapy, 14/20 (70%) with mobile cords had continuing local control, compared with 11/18 (61%) of those with persisting fixation [17]. A further 4/7 (57%) patients with impaired mobility at this same time following treatment also had continuing local control. However, 6 of the 11 patients with local control and persisting cord fixation 1 month following radiotherapy subsequently had return of cord mobility. Therefore 20 of the 29 patients with local control had eventual return of cord mobility. This is not dissimilar from the Cardiff patients, of whom 23 remained recurrence free at 5 years,

18 of these having mobile cords [29]. In summary, most patients with local control following radiotherapy for T3 glottic cancer will have eventual return of cord mobility but persisting cord fixation does not provide a clinically useful predictive indicator.

VARIABLES POTENTIALLY INFLUENCING RADIOTHERAPY SEQUELAE

Factors related to the delivery of radiotherapy, in particular the volume of tissue treated, the total dose and fractionation schedule, and site and stage of disease, have been implicated in affecting the incidence of significant postradiotherapy normal tissue reactions. In a randomised study analysing the effect of a 1 × 1-cm increase in treatment volume for T1 glottic carcinoma, the incidence of arytenoid oedema persisting for more than 6 months was 11% for the larger field size and 2% for the smaller ($P < 0.02$) [35]. This was also a significant increase in the severity of acute mucositis in patients treated with the larger volume (6 × 6 cm). This study, which originally aimed to assess the effect of such a variation of treatment volume on tumour control, provides an elegant demonstration of the importance of volume.

The influence of fractionation in the determination of late effects has become increasingly clear. This was well demonstrated in a review of patients with early glottic cancer, from one centre, treated with either a hypofractionated (large doses per fraction) regimen or more standard dose (2 Gray) per fraction [19]. There was a 23% incidence of severe oedema or necrosis in the hypofractionated group compared with 3% in the standard group. Stage of disease has also been implicated along with laryngeal subsite in increasing the risk of radiotherapy sequelae [13,17,24]. More advanced-stage disease or supraglottic subsite is often treated using a larger volume or higher dose, or both, making it difficult to determine which variable is the most important. At least two groups have shown increasing total dose to be associated with an increased risk of perichondritis or edema [3,31]. More recently, attempts have been made to improve on the results of standard fractionation, either by increasing the total dose with multiple small fractions per day or decreasing the overall treatment time. Many of these regimens have not resulted in increased late effects, but some earlier studies with an inadequate interfraction interval have noted such an increase [36–39]. Surgeons should be aware if their centre is participating in a study of altered fractionation as the data from Table II may not necessarily be applicable.

Irritant factors such as continued smoking and chronic respiratory tract infections have also been implicated in exacerbating the late effects of radiotherapy on the larynx [26]. Continued smoking would intuitively seem to be associated with an increased risk of late normal tissue reactions after radiotherapy, but in a study of acute mucosal reactions no such effect was seen [40]. Most radiation oncologists have, however, seen the benefits of smoking cessation on the upper aerodigestive mucosa following radiotherapy.

ROLE OF RADIOLOGY IN DISTINGUISHING TUMOUR RECURRENCE FROM RADIOTHERAPY SEQUELAE

Computed tomography (CT) has proved to be a useful tool in the delineation of the extent of laryngeal carcinoma at presentation. The confirmation of its accuracy has come through the comparison of preoperative imaging with sectioned operation specimens [41]. Unfortunately, the same cannot be said for CT in the evaluation of the patient following radiotherapy where it is often difficult to detect residual tumour, or rather distinguish it from radiotherapy sequelae such as oedema and necrosis [41]. Positron emission tomography (PET) with fluorodeoxyglucose may hold some promise in this difficult clinical situation, similar to its role in the evaluation of patients after radiotherapy for brain tumours, where radionecrosis can mimic recurrence [42]. Greven et al. [43] performed PET scans on 11 patients suspected of having persistent or recurrent laryngeal carcinoma after radiotherapy. Five cases had clinical evidence of persistent laryngeal oedema. In 4 of these 5 cases, the PET scan did not indicate recurrence, with 1 scan equivocal. One of these patients underwent laryngectomy for suspected neck recurrence, with the operative specimen showing no evidence of disease in the primary site. The other 4 patients have been followed for up to 14 months without developing clinical evidence of recurrence. Further data evaluating the role of PET with fluorodeoxyglucose in this clinical situation will be needed to confirm these findings.

CONCLUSIONS

Detection of recurrent or residual laryngeal carcinoma in the presence of significant postradiotherapy sequelae remains difficult. Approximately 50% of patients with severe oedema or necrosis after radiotherapy will harbour underlying tumour. Head and neck surgeons performing salvage procedures after radiotherapy will, on average, remove one larynx containing no evidence of tumour for every 11 with recurrence. PET scanning with fluorodeoxyglucose holds some promise in better identifying patients who can be treated conservatively, especially when the functional status of the larynx is good.

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